

AMU-A134 545

TOXICOLOGICAL ASSESSMENT OF ABATE (TRADENAME)  
(000'0'-TETRAMETHYL-00'-THI..(U) ARMY ENVIRONMENTAL  
HYGIENE AGENCY ABERDEEN PROVING GROUND MD

1/1

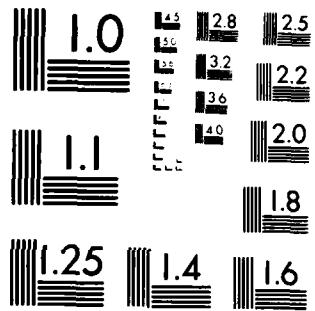
UNCLASSIFIED

R A ANGERHOFER ET AL. 02 NOV 83

F/G 6/20

NL

END  
DATE  
FILED  
11-83  
DTIC



MICROCOPY RESOLUTION TEST CHART  
NATIONAL BUREAU OF STANDARDS 1963 A

(12)

AD - A134545



UNITED STATES ARMY  
ENVIRONMENTAL HYGIENE  
AGENCY

ABERDEEN PROVING GROUND, MD 21010

A  
E  
H  
A

PHASE 4  
STUDY NO. 75-51-1302-84  
TOXICOLOGICAL ASSESSMENT OF ABATE•  
(0,0,0',0'-TETRAMETHYL-0,0'-THIO-DI-P-PHENYLENE PHOSPHOROTHIOATE)  
ADMINISTERED ORALLY AND DERMALLY  
TO MATED FEMALE RABBITS  
APRIL 1983

Approved for public release; distribution unlimited.

DTIC FILE COPY

DTIC  
SELECTED  
S NOV 08 1983  
D  
E

83

32

## UNCLASSIFIED

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM															
1. REPORT NUMBER 75-51-1302-84	2. GOVT ACCESSION NO. AD-A134545	3. RECIPIENT'S CATALOG NUMBER															
4. TITLE (and Subtitle) Phase 4, Toxicological Assessment of ABATE® (0,0,0',0'-Tetramethyl-0,0'-Thio-Di-P-Phenylene Phosphorothioate) Administered Orally and Dermally to Mated and Nonmated Female Rabbits, Study No. 75-51-1302-84, April 1983		5. TYPE OF REPORT & PERIOD COVERED Final, Sep 1979 - Aug 1983															
7. AUTHOR(s) Richard A. Angerhofer Maurice H. Weeks		6. PERFORMING ORG. REPORT NUMBER 110															
9. PERFORMING ORGANIZATION NAME AND ADDRESS Commander US Army Environmental Hygiene Agency Aberdeen Proving Ground, MD 21010		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS															
11. CONTROLLING OFFICE NAME AND ADDRESS Commander US Army Health Services Command Ft Sam Houston, TX 78234		12. REPORT DATE Sep 1979 - Aug 1983															
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)		13. NUMBER OF PAGES 45															
		15. SECURITY CLASS. (of this report) Unclassified															
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE															
16. DISTRIBUTION STATEMENT (of this Report) Approved for public release; distribution unlimited.																	
17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)																	
18. SUPPLEMENTARY NOTES																	
19. KEY WORDS (Continue on reverse side if necessary and identify by block number) <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%;">ABATE®</td> <td style="width: 33%;">Pediculicide</td> <td style="width: 33%;">0,0,0',0'-Tetramethyl-0,0'-Thio-Di-P-</td> </tr> <tr> <td>Cholinesterase</td> <td>Pregnancy</td> <td>Phenylene Phosphorothioate</td> </tr> <tr> <td>Dermal Administration</td> <td>Rabbit</td> <td></td> </tr> <tr> <td>Gestation</td> <td>Teratogenic</td> <td></td> </tr> <tr> <td>Oral Administration</td> <td>Teratology</td> <td></td> </tr> </table>			ABATE®	Pediculicide	0,0,0',0'-Tetramethyl-0,0'-Thio-Di-P-	Cholinesterase	Pregnancy	Phenylene Phosphorothioate	Dermal Administration	Rabbit		Gestation	Teratogenic		Oral Administration	Teratology	
ABATE®	Pediculicide	0,0,0',0'-Tetramethyl-0,0'-Thio-Di-P-															
Cholinesterase	Pregnancy	Phenylene Phosphorothioate															
Dermal Administration	Rabbit																
Gestation	Teratogenic																
Oral Administration	Teratology																
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) <p>This study was designed to assess the teratologic potential of ABATE® following repeated oral or dermal administration of the compound to pregnant rabbits during the major period of organogenesis. There were no teratologic effects in New Zealand White rabbits associated with repeated oral or dermal administration of ABATE at levels which produced a toxic effect. Although these studies have shown that ABATE should not cause teratogenic effects in its intended use, chronic studies should be performed to further define any potential long term toxicity.</p>																	



DEPARTMENT OF THE ARMY Mr. Angerhofer/or1/AUTOVON  
U.S. ARMY ENVIRONMENTAL HYGIENE AGENCY  
ABERDEEN PROVING GROUND, MARYLAND 21010

REPLY TO  
ATTENTION OF

HSHB-OT/WP

2 Nov 1983

SUBJECT: Phase 4, Study No. 75-51-1302-84, Toxicological Assessment of ABATE® (0,0,0',0'-Tetramethyl-0,0'-Thio-Di-P-Phenylene Phosphorothioate) Administered Orally and Dermally to Mated Female Rabbits, April 1983

Executive Secretary  
Armed Forces Pest Management Board  
Forest Glen Section, WRAMC  
Washington, DC 20307

#### EXECUTIVE SUMMARY

The purpose, essential findings, and major recommendations of the inclosed report follow:

a. Purpose. The purpose of this study was to assess the teratologic potential of ABATE® following repeated oral or dermal administration of the compound to pregnant rabbits during the major period of organogenesis.

b. Essential Findings. There were no teratologic effects in New Zealand White rabbits associated with repeated oral or dermal administration of ABATE at levels which produced a toxic effect.

c. Major Recommendations. Perform chronic studies to determine any potential hazard associated with long term use of ABATE. These studies have shown that ABATE does not cause teratologic effects in laboratory rabbits.

FOR THE COMMANDER:

1 Incl  
as

for Robert W. Clark  
JOEL C. GADDIS, M.D.  
Colonel, MC  
Director, Occupational and Environmental Health

CC:  
HQDA (DASG-PSP) wo incl  
Cdr, HSC (HSPA-P)  
Comdt, AHS (HSHA-IPM)  
Dir, Advisory Ctr Div Tox, NRC (2 cy)  
USDA, ARS, Southern Region (3 cy)  
USDA, ARS, Southern Region (COL Moussa)  
USDA, ARS (Dr. Terrence McGovern)



Accession For	
NTIS GRA&I	<input checked="" type="checkbox"/>
DTIC TAB	<input type="checkbox"/>
Unannounced	<input type="checkbox"/>
Justification	<input type="checkbox"/>
By _____	
Distribution	
Availability: Sales	
Dist	Available for Special
A-1	

Phase 4. Toxicological Assessment of ABATE, Study No. 75-51-1302-84, Apr 83

CONTENTS

Paragraph	Page
1. AUTHORITY.....	1
2. REFERENCE.....	1
3. PURPOSE.....	1
4. SUMMARY AND CONCLUSION.....	2
5. BACKGROUND.....	3
6. MATERIALS AND METHODS.....	4
7. RESULTS.....	8

APPENDIX

A - Summary of Maternal and Fetal Parameters.....	A-1
B - Examination of Skeletal and Soft Tissue Structures for Malformations and Variations.....	B-1
C - Individual Maternal and Fetal Parameters - Group IV Dermal Pyrax Control.....	C-1
D - Individual Maternal and Fetal Parameters - Group V Dermal Pyrax with 10 Percent ABATE.....	D-1
E - Individual Maternal and Fetal Parameters - Group VI Dermal Technical ABATE.....	E-1
F - Individual Maternal and Fetal Parameters - Group VII Oral Technical ABATE.....	F-1
G - Individual Maternal and Fetal Parameters - Group VIII Intraperitoneal 6-AN.....	G-1
H - Individual Maternal and Fetal Parameters - Group IX Dermal Pyrax with 2 Percent ABATE.....	H-1
I - Mean Body Weights (kg) - Female Rabbits.....	I-1
J - Statistical Analysis of Body Weight Changes.....	J-1
K - Individual Maternal Body Weights (kg) - Group IV Dermal Pyrax Control.....	K-1
L - Individual Maternal Body Weights (kg) - Group V Dermal Pyrax with 10 Percent ABATE.....	L-1
M - Individual Maternal Body Weights (kg) - Group VI Dermal Technical ABATE.....	M-1
N - Individual Maternal Body Weights (kg) - Group VII Oral Technical ABATE.....	N-1
O - Individual Maternal Body Weights (kg) - Group VIII Intraperitoneal 6-AN.....	O-1
P - Individual Maternal Body Weights (kg) - Group IX Dermal Pyrax with 2 Percent ABATE.....	P-1
Q - RBC Cholinesterase Activity - Comparison with Time of Various Treatments with Pyrax Control.....	Q-1
R - Individual Maternal RBC Cholinesterase Activity - Group IV Dermal Pyrax Control.....	R-1
S - Individual Maternal RBC Cholinesterase Activity - Group V Dermal Pyrax with 10 Percent ABATE.....	S-1
T - Individual Maternal RBC Cholinesterase Activity - Group VI Dermal Technical ABATE.....	T-1
U - Individual Maternal RBC Cholinesterase Activity - Group VII Oral Technical ABATE.....	U-1
V - Individual Maternal RBC Cholinesterase Activity - Group VIII Intraperitoneal 6-AN.....	V-1

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84, Apr 83

Paragraph	Page
W - Individual Maternal RBC Cholinesterase Activity - Group IX Dermal Pyrax with 2 Percent ABATE.....	W-1
X - Plasma Cholinesterase Activity - Comparison with Time of Various Treatments with Pyrax Control.....	X-1
Y - Individual Maternal Plasma Cholinesterase Activity - Group IV Dermal Pyrax Control.....	Y-1
Z - Individual Maternal Plasma Cholinesterase Activity - Group V Pyrax with 10 Percent ABATE.....	Z-1
AA - Individual Maternal Plasma Cholinesterase Activity - Group VI Dermal Technical ABATE.....	AA-1
BB - Individual Maternal Plasma Cholinesterase Activity - Group VII Oral ABATE.....	BB-1
CC - Individual Maternal Plasma Cholinesterase Activity - Group VIII Intraperitoneal 6-AN.....	CC-1
DD - Individual Maternal Plasma Cholinesterase Activity - Group IX Dermal Pyrax with 2 Percent ABATE.....	DD-1
EE - Maternal Brain Cholinesterase Activity at Termination of Pregnancy.....	EE-1
FF - Maternal Brain Cholinesterase activity - Comparison of Various Treatments with Pyrax Control.....	FF-1
GG - Mean Fetal Body Weight and Length Per Doe.....	GG-1
HH - Bibliography.....	HH-1



DEPARTMENT OF THE ARMY  
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY  
ABERDEEN PROVING GROUND, MARYLAND 21010

REPLY TO  
ATTENTION OF  
HSHB-OT/WP

PHASE 4  
STUDY NO. 75-51-1302-84  
TOXICOLOGICAL ASSESSMENT OF ABATE<sup>•</sup>  
(0,0,0',0'-TETRAMETHYL-0,0'-THIO-DI-P-PHENYLENE PHOSPHOROTHIOATE)  
ADMINISTERED ORALLY AND DERMALLY  
TO MATED FEMALE RABBITS  
APRIL 1983

1. AUTHORITY. Letter, HSPA-H, US Army Health Services Command, 20 October 1976, subject: Investigational New Drug Application for ABATE Pediculicide, with Inclosure, letter, AFPCB, Armed Forces Pest Control Board, 13 September 1976, same subject.

2. REFERENCES.

a. Memorandum for Record, SGRD-UWF-B, Walter Reed Army Institute of Research, 18 July 1978, subject: ABATE Pediculicide.

b. Letter, HSE-LT, this Agency, 5 December 1977, subject: Investigational New Drug Application for ABATE Pediculicide (Phase I).

c. Letter, HSE-LT, this Agency, 23 April 1980, subject: Phase 2, Toxicological Assessment of ABATE (0,0,0',0'-Tetramethyl-0,0'-Thio-Di-P-Phenylene Phosphorothioate), Dermal Penetration of Radio-Labeled ABATE, Study No. 75-51-1302-80, September 1977- October 1979.

d. Letter, HSHB-LT-T/WP, this Agency, 27 September 1983, subject: Phase 3, Study No. 75-51-1302-83, Toxicological Assessment of ABATE<sup>•</sup> (0,0,0',0'-Tetramethyl-0-,0'-Thio-Di-P-Phenylene Phosphorothioate) Administered Orally to Mated and Nonmated Rabbits, April 1983.

3. PURPOSE. This teratologic study in rabbits is designed according to the 1966 "Guidelines for Reproduction Studies for Safety Evaluation of Drugs for Human Use" distributed by FDA. The data provided by the examination of fetuses derived from rabbits treated with ABATE during the critical period of gestation will aid in estimating the teratogenic potential, if any, of that compound. The experimental design for this study is shown in Table 1.

<sup>•</sup>ABATE is a registered trademark for American Cyanamid Co., Princeton, New Jersey 08540.

Use of trademarked names does not imply endorsement by the US Army, but is intended only to assist in identification of a specific product.

Approved for public release; distribution unlimited.

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84, Apr 83

4. SUMMARY AND CONCLUSION. Studies were conducted to evaluate the potential for ABATE to produce embryotoxic or teratogenic effects in pregnant rabbits after dermal or oral administration during the 6th through 18th day of pregnancy. The ABATE preparations and dosages used in this study were:

Dermal:

Pyrax® Powder Control	0 mg/kg/day
Pyrax Powder (10-percent ABATE)	163 mg/kg/day
Pyrax Powder (2-percent ABATE)	16.3 mg/kg/day
Technical Grade ABATE	164 mg/kg/day

Oral:

Technical Grade ABATE in 10-percent aqueous acacia	32 mg/kg/day
---	--------------

Intraperitoneal:

Positive Control [6-Aminonicotinamide (6-AN)] Day 9 only	4 mg/kg
---	---------

Under the conditions of the experiment, the following parameters were found to be affected:

- a. Significant decreases were found in RBC cholinesterase activity in animals receiving Pyrax powder containing 10-percent ABATE dermally (163 mg/kg/day) and technical ABATE dermally and orally (164 mg/kg/day and 32 mg/kg/day, respectively).
- b. The gestation index showed only a slight (17 and 11 percent) decrease in animals receiving technical ABATE orally and dermally, while the positive control caused a significant decrease in that index.
- c. The fertility index was lower than controls, for animals receiving 10 percent ABATE in Pyrax powder dermally. This finding was not statistically significant.
- d. Technical ABATE, at a dosage of 164 mg/kg/day, dermally, was toxic to pregnant does, causing death in 6 of 15 rabbits. This dosage was also embryotoxic, causing a decrease in total implants, decreased total alive fetuses and a significant decrease in average fetal weight when compared to fetuses from Pyrax powder controls.

---

• Pyrax is a registered trademark of R. T. Vanderbilt Company, Inc., New York, New York 10017.

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84, Apr 83

e. The positive control, 6-AN, caused a decrease in the total number of fetuses and fetuses per doe, a decrease in live fetuses and live fetuses per doe, a significant increase in resorptions and resorptions per doe, early resorptions, total malformations and malformation index. The average fetal weight was significantly decreased compared to fetuses from Pyrax powder controls.

f. No teratologic effects were observed in fetuses from rabbit does receiving ABATE as the technical grade compound or as Pyrax powder formulations

g. These tests indicated no teratologic hazard in New Zealand White rabbits following repeated application of ABATE at levels which produced toxic effects by both dermal and oral routes.

5. BACKGROUND.

a. The Armed Forces Pest Management Board (AFPMB), formerly the Armed Forces Pest Control Board, is coordinating the registration of ABATE as a pediculicide with the Food and Drug Administration (FDA), since a formulation of this compound is proposed for standardization for the control of lice in military programs. Negotiations with FDA for a field test program for this preparation have indicated the need for the development of an Investigational New Drug Application (IND). The only formulation for which FDA registration is to be sought is 2-percent ABATE, 98-percent Pyrax. The target species are:

- (1) The body louse, Pediculus humanus humanus (L).
- (2) The head louse, Pediculus humanus capitis (DeGeer).
- (3) The pubic louse, Pthirus pubis (L).

b. To assist in the development of this IND, the US Army Environmental Hygiene Agency (USAEEHA) was requested to conduct a teratology study in a second mammalian species, namely the rabbit (see paragraph 1, this report).

c. The proposed patterns of military use for 2-percent ABATE pediculicide encompass both group and individual treatment. The group method involves the treatment of infested individuals by operators using power-driven or manually operated equipment. It is estimated that the group application method results in the application of approximately 31 grams of formulated dust (0.62 gm active ingredient) per individual.

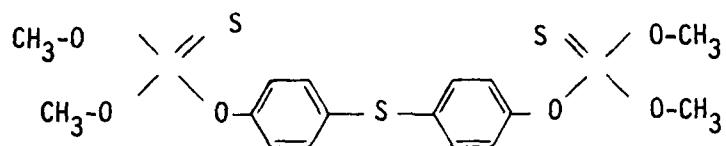
d. The individual treatment method involves self-treatment. For this purpose, the dust is packaged in 2-ounce (56.7 gm) shaker cans. Instructions will indicate that the entire contents of the can be used for heavy infestations and the amount to be applied may thus be 56.7 gm of formulated powder (1.134 gm ABATE).

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84, Apr 83

6. MATERIALS AND METHODS.

a. Chemicals.

(1) The experimental insecticide ABATE (0,0,0',0'-thio-di-p-phenylene phosphorothioate), CAS Number 003383-96-8, is a reddish-amber viscous liquid ( $d_{25} = 1.587$ ), with a foul odor. It is also identified or known as Bithion, Difenthos, ENT-27165, Experimental Insecticide 52160 and Temephos. It is soluble in acetone, carbon tetrachloride, ether, ethylene dichloride and toluene. It is insoluble in hexane, methyl cyclohexane and water. The molecular weight is 466.48; its empirical formula is  $C_{16}H_{20}O_6P_2S_3$  and its structural formula is shown below:



The material used in these studies was supplied by American Cyanamid Company, Agricultural Division, Princeton, New Jersey, and was contained in a labeled plastic bottle. The label contained a warning statement and the name ABATE, Technical Insecticide, Active Ingredients: Temephos [0,0' (thiodi-4, 1-phenylene) bis (0,0'-dimethyl phosphorothioate)] 90 percent w/w Inert Ingredient 10 percent and lot identification number L3402 R3 6/76 WG.

(2) Pyrax powder was received by this laboratory from Insects Affecting Man Research Laboratory, US Department of Agriculture, Agricultural Research Service, PO Box 14565, Gainesville, Florida 32604. The original source of the material was R.T. Vanderbilt Company, Inc., 230 Park Avenue, New York 10017. Pyrax is their tradename for pyrophyllite, a hydrous aluminum silicate.

(3) Acacia, U.S.P. (Gum Arabic) - F.C.C., Food Grade (No. 5-0430, Lot No. 421152), was procured from J.T. Baker Chemical Co., Phillipsburg, New Jersey 08865.

(4) 6-AN (Catalog No. A-630, Lot No. 24C0920) was purchased from Sigma Chemical Co., St Louis, Missouri.

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84, Apr 83

b. Animals. Three groups of 45 each, sexually mature, dated pregnant, female New Zealand White rabbits were purchased from Marland Breeding Farms, Inc., PO Box X, Hewitt, New Jersey 07421. The rabbits were dated from time of mating, weighed between 2.9 and 3.8 kg and were received on Day 4 of gestation. The day of mating is defined as Day 0 of gestation. The three groups were received in separate shipments at 45 day intervals. Each group of 45 rabbits was randomized and subdivided into three groups of 15 rabbits each. Animals were housed in individual cages (Porter-Mathews, 16 inches X 18 inches X 24 inches) and received laboratory diet (Rabbit Ration NIH 09, Zeigler Brothers, Inc., PO Box 95, Gardners, Pennsylvania 17321) and tap water ad libitum. The room temperature was kept at  $23 \pm 1^{\circ}\text{C}$ , relative humidity 45-55 percent and were maintained on a 12-hour light/dark sequence (see Table 1, Experimental Design).

c. Preparation of Solutions.

(1) The 10-percent aqueous solutions of gum acacia were used as a vehicle control and to suspend the technical ABATE (90 mg/ml) for the oral dosing. It was also used to suspend 6-AN (100 mg/ml), the positive control for teratogenic effects.

(2) The ABATE dust formulation under consideration is a mixture of the chemical with Pyrax powder. A 2 kg unformulated lot of Pyrax powder was received from Insects Affecting Man Research Laboratory, Gainesville, Florida, as well as 2 kg of a 10-percent (w/w) ABATE/Pyrax formulation (244.4 gm technical ABATE in 1755.56 gm pyrax powder). The ABATE dust formulation was prepared by mixing pyrax with acetone (certified A.C.S grade, Fisher Scientific) and ABATE to make a slurry. The mixture was placed under a hood to allow the acetone to evaporate. The dried material was then pulverized with mortar and pestle.

(3) The 2 percent (w/w) ABATE/Pyrax mixture was prepared by USAEHA using acetone (A.C.S, National Stock No. 6810-00-264-8955, DSA-400-75-C-44 64, Lot 1 from ASP, Inc., Landston, Virginia 23150) as described previously, but using 22 gm of the technical grade ABATE with 1002 gm of Pyrax powder and adding sufficient acetone for the slurry.

(4) Gravimetric analyses of the two ABATE/Pyrax formulations by the Organic Environmental Chemistry Division (OECD), USAEHA, showed the 10 percent mixture to contain 10.19-percent ABATE (OECD Log Number 5254). The 2-percent mixture contained 2.3-percent ABATE (OECD Log Number 5255).

d. Treatment Schedule. Under FDA Guidelines, mated female rabbits were dosed daily from Day 6 through Day 18 of gestation. Doses were adjusted each day according to body weight. All treatments followed the daily routine of gestation Days 6-18 except for the intraperitoneal dose of 6-AN which was given on Day 9 only.

(1) The oral dosage of 32 mg/kg was based on a preliminary range-finding study in rabbits. In that study, several concentrations of

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84, Apr 83

TABLE 1. EXPERIMENTAL DESIGN

GROUP	TREATMENT	FORMULATION	DOSAGE	TREATMENT SCHEDULE (DAYS OF PREGNANCY)	NO. OF RABBITS
I	<u>Exposed, oral</u> - suspension of technical grade ABATE	90 mg ABATE/mL 10% aqueous Acacia	32 mg ABATE/kg/day	6-18	15
II	<u>Control, oral</u> - solutions of aqueous 10% Acacia	10% aqueous Acacia	0.5 mL/kg/day	6-18	15
III	<u>Positive Control</u> - Intra-peritoneal administration of 6-AN	100 mg 6-AN/mL 10% aqueous Acacia	2.5 mg 6-AN/kg	Day 9	15
IV	<u>Control Dust</u> - dermal application untreated Pyrax		1.81 gm Pyrax/kg/day	6-18	15
V	<u>Exposed Dust</u> - dermal application 10% ABATE in Pyrax	100 mg ABATE/gm Pyrax	163 mg ABATE/kg/day	6-18	15
VI	<u>Exposed Dermal</u> application technical grade ABATE		164 mg ABATE/kg/day	6-18	15
VII	<u>Exposed, oral</u> - suspension of technical grade ABATE	90 mg ABATE/mL 10% aqueous Acacia	32 mg ABATE/kg/day	6-18	15
VIII	<u>Positive Control</u> - Intra-peritoneal administration of (6-AN)	100 mg 6AN/mL 10% aqueous Acacia	4.0 mg 6-AN/kg	Day 9	15
IX	<u>Exposed Dust</u> - dermal application 2% ABATE in Pyrax	20 mg ABATE/gm Pyrax	16.3 mg ABATE/kg/day	6-18	15

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84, Apr 83

ABATE in 10-percent gum acacia were given daily by the oral route to determine a dosage which would lower plasma and RBC cholinesterase levels to about 50 percent of the pretreatment levels.

(2) The 10-percent ABATE/Pyrax formulation and the dermal application of technical grade compound were treatments at dosages which were approximately 10 times the projected single, manual human use treatment on a mg per kg basis.

(3) The 2-percent ABATE/Pyrax formulation approximated the projected single, manual, human-use treatment.

(4) The dosage for 6-AN was based on an extrapolation from data in an article by Schardein, et al<sup>1</sup>.

e. Test Procedure.

(1) Mated animals were received on Day 4 of gestation. Treatment was initiated on Day 6 and continued through Day 18 of gestation for all groups except those receiving the single intraperitoneal dosage of 6-AN on Day 9.

(2) Daily observations for toxicologic signs were made. All rabbits were weighed on Day 4; Days 6-18; Days 22, 25, 28 and 30. Animals were bled from the central ear artery on Days 5, 7, 19 and 30 of gestation for determination of plasma and erythrocyte (RBC) cholinesterase activity. These clinical chemistry analyses were performed according to the method described by Garry and Routh<sup>2</sup>. All animals were sacrificed on Day 30 of gestation by means of an intravenous overdose of barbiturate. At this time, the brains were removed from two fetuses from each litter for the determination of brain cholinesterase activity. The brains from all does were also analyzed for cholinesterase activity.

(3) The examination of fetuses for malformations was conducted according to the method of Wilson and Warkany<sup>3</sup>. The post mortem for each doe consisted of counting the conceptuses: number, location, living, dead, early resorption and late resorption. All fetuses were tagged for identification, weighed, measured and examined for external defects. Approximately one-third (1/3) of the fetuses were fixed in Bouin's fluid<sup>4</sup> and examined by the Wilson technique for neural and visceral defects<sup>3</sup>. The remaining two-thirds (2/3) of the fetuses were placed in 95 percent ethyl alcohol, cleared and their skeletons stained with alizarin red S and examined for the presence of anomalies<sup>5</sup>.

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84, Apr 83

f. Evaluation of Data.

(1) Definition of Terms. The following indices were calculated. Results appear in Appendices A-H.

Index of fertility:	$\frac{\text{pregnant animals}}{\text{total number of mated animals}}$	X 100
Index of viable births:	$\frac{\text{alive normal fetuses}}{\text{total number of fetuses}}$	X 100
Index of dead births:	$\frac{\text{dead normal fetuses}}{\text{total number of fetuses}}$	X 100
Index of resorptions:	$\frac{\text{total number of resorptions}}{\text{total number of implantations}}$	X 100
Index of variations:	$\frac{\text{total number of variations}}{\text{total number of fetuses}}$	X 100
Index of malformations:	$\frac{\text{total number of malformations}}{\text{total number of fetuses}}$	X 100
Index of gestation:	$\frac{\text{total number of litters}}{\text{total number of females pregnant}}$	X 100

Variations: All runts and anomalies.

Early resorptions: Placental remains only.

Late resorptions: Placental and fetal remnants.

Runts: A fetus weighing 70 percent or less of the average weight of its litter.

(2) Statistical Analysis. Applicable fetal parameters, cholinesterase values and body weights were analyzed statistically using the Student's "t" test with significance selected at the 0.05 level of probability.

7. RESULTS.

a. Exclusion of Test Groups. Data from rabbit groups I, II, and III are considered inadequate and are not reported or discussed. Dosing methods resulted in a high percentage of maternal deaths in groups I (11/15) and II (13/15) by the end of the study. This high mortality rate resulted in an insufficient number of animals reaching term and it was decided that such a sample size was too small upon which to base any conclusions. Similarly, the positive control Group III received a 0.3 mg/kg dosage of 6-AN, intraperitoneally, on Day 9 of gestation instead of 3.0 mg/kg. Data from this group was also considered incomplete and invalid and was not included in the body of the study.

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84, Apr 83

b. The following results are given for Groups IV through IX:

(1) Maternal Parameters.

(a) Clinical Picture of Females. Animals of all groups were received in good condition and showed a smooth, shiny hair coat. A few had diarrhea for 2-3 days after arrival, but this condition soon disappeared and the fecal pellets appeared normal for the duration of the test period.

(b) Weight Gain of Females. Body weights remained essentially, unchanged or showed slight gain during the treatment period (Days 6-18 of gestation). These data are summarized in Appendix I. Individual data are presented in Appendices J-P.

(c) Toxicity. Repeated treatment of rabbits with dermal or oral administration of technical grade ABATE caused toxic responses with deaths occurring in each group of animals. No skin irritation resulted from dermal application of technical grade ABATE or the Pyrax formulations.

(d) Cholinesterase Activity. Oral and dermal application of technical grade ABATE and Pyrax with 10-percent ABATE caused a significant reduction in RBC cholinesterase activity after 13 days of treatment. This activity remained depressed in these groups at sacrifice. Maternal brain cholinesterase activity was not affected in any treatment group. Plasma cholinesterase activity was depressed after 13 days of treatment with dermal application of technical grade ABATE and Pyrax with 10-percent ABATE. The plasma cholinesterase activity following oral ABATE treatment indicated a decreasing trend, but was not statistically significant ( $p < .05$ ). Plasma cholinesterase activity in dermal technical ABATE rabbits remained depressed at sacrifice. Plasma and RBC cholinesterase activities were not depressed in the 2-percent ABATE pyrax group. Cholinesterase data are presented in Appendices Q-FF.

(e) Gestation and Fertility Indices. The gestation index was significantly reduced in the 6-AN group and was reduced by 11 and 17 percent in the dermal and oral technical grade ABATE groups respectively. The fertility index was reduced in the group receiving dermally applied Pyrax with 10-percent ABATE.

(f) Necropsy Findings. No gross changes in tissues or organs of the female rabbits were found at necropsy.

(2) Fetal Parameters.

(a) Index of Dead and Live-born Fetuses. No differences of biological relevance were found upon comparison of the groups.

(b) Implantations. Implantations per doe were 21 percent lower than Pyrax controls in does receiving technical grade ABATE dermally. This finding is not considered to be compound related since implantation would have occurred prior to the start of treatment.

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84, Apr 83

(c) Index of Resorptions. Resorption sites were found in does from all treatment groups. As expected, the positive control group had a much greater number of resorptions than test or negative control groups.

(d) Abnormalities/Anomalies. All true malformations (soft tissue or skeletal defects such as gastroschisis, exencephaly, cleft palate) are classified as abnormalities. Anomalies are considered to be minor variants from the normal, such as unossified sternebrae and retarded ossification of the fontanella. A single malformed fetus from each of Groups IV, V and VII is considered to be a natural occurrence and not related to the test compound. The number of variants showed no compound related differences. Group VIII, given the known teratogen 6-AN, showed an expected high incidence of malformations. A summary of fetal examination findings is presented in Appendix E.

(e) Average Number of Fetuses. Group VIII (6-AN) showed a significant decrease in the absolute total of fetuses and the mean number of fetuses per doe. Group VI (dermal technical ABATE) showed some reduction in the total and mean number of fetuses, but this is considered to be an expression of the maternal and fetal toxicity of dermally applied technical grade ABATE.

(f) Average Fetal Weight. Significant differences were found between control and test fetuses from the dermal technical ABATE and 6-AN groups. No differences between control and the remaining treatment groups occurred at  $p < .05$ . Data on fetal size is presented by litter in Appendix GG.

*Richard A. Angerhofer*

RICHARD A. ANGERHOFER  
Biologist  
Toxicology Division

*Maurice H. Weeks*

MAURICE H. WEEKS  
Chief, Toxicology Division

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

APPENDIX A  
SUMMARY OF MATERNAL AND FETAL PARAMETERS

	Dermal Pyrax Control IV	Dermal Pyrax 10% ABATE V	Dermal Technical ABATE VI	Oral ABATE VII	I.P.-6-AN Positive Control VIII	Dermal Pyrax 25 ABATE IX
Females mated	13	14	8	10	14	12
Females pregnant	10	9	6	9	11	10
Index of Fertility (%)	77	64	75	90	79	83
Litters	10	9	5	8	5	10
Index of Gestation (%)	100	100	83	89	45*	100
Implantations total	94	96	47	89	99	113
Implantations per doe	9.40	10.67	7.83	9.89	9.00	11.30
Fetuses, total	87	82	33	65	16	92
Fetuses per doe	8.70	9.11	5.50	7.22	1.45*	9.20
Alive fetuses, total	86	81	33	65	16	92
Alive fetuses per doe	8.60	9.00	5.50	7.22	1.45*	9.20
Index of viable fetuses (%)	98.85	97.59	100	100	100	100
Dead fetuses, total	1	1	0	0	0	0
Dead fetuses per doe	0.10	0.11	0	0	0	0
Index of dead births (%)	1.15	1.23	0	0	0	0
Resorptions, total	7	14	14	24	83	21
Resorptions per doe	0.70	1.56	2.33	2.67	7.55*	2.10
Index of Resorptions (%)	7.45	14.58	29.79	26.97	83.84*	18.58
Early resorptions	4	10	14	24	83	20
Late resorptions	3	4	0	0	0	1
Variants, total	4	2	2	3	1	0
Variants per doe	0.40	0.22	0.33	0.33	0.09	0
Index of variations (%)	4.60	2.61	6.06	4.62	6.25	0
Malformations, total	1	3	0	1	53	0
Index of Malformations (%)	1.15	3.61	0	1.54	331*	0
Runts	2	1	2	1	1	0
Average fetus weight (g)	46.20	48.60	40.80*	49.70	37.60*	52.40

\* Significantly different from dermal pyrax control at .05 level of probability.

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

APPENDIX B

EXAMINATION OF SKELETAL AND SOFT TISSUE STRUCTURES  
FOR MALFORMATIONS AND VARIATIONS

Animal No.	Observations	Fetus Quantity	Fetus Quality
Group IV (Control)			
48	talipes equinovarus	1	■
52	parietal bones overlap frontals	1	▼
Group V (Dermal Pyrax 10% ABATE)			
90	anencephalia	1	■
	thoracoschisis	1	■
	gastroschisis	1	■
Group VII (Oral technical ABATE)			
94	enlarged fontanella	1	▼
95	parietal bones overlap frontals	1	▼
105	tibias, fibulas and femurs not completely formed	1	■
Group VIII (IP-6-AN)			
107	spina bifida	1	■
	microphthalmia	5	■
	cleft palate	3	■
	talipes equinovarus	5	■
	gastroschisis	1	■
	fused ribs	2	■
113	microphthalmia	3	■
	talipes equinovarus	3	■
	gastroschisis	1	■
	fused ribs	2	■
114	spina bifida	1	■
	microphthalmia	2	■
	cleft palate	1	■
	craniocleisis	1	■
	gastroschisis	1	■
	webbed feet	1	■
	fused ribs	1	■
118	microphthalmia	3	■
	cleft palate	2	■
	talipes equinovarus	1	■
120	microphthalmia	3	■
	cleft palate	3	■
	craniocleisis	1	■
	hydrocephalia	1	■
	talipes equinovarus	2	■
	fused ribs	1	■
	frontal & parietal bones deformed	2	■

▼ = variation  
■ = malformation

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

APPENDIX C

INDIVIDUAL MATERNAL AND FETAL PARAMETERS  
GROUP IV  
DERMAL PYRAX CONTROL

Animal No.	Mated	Pregnant	Implantations	Resorptions	Total No. Late of Fetuses	Dead	Alive Malformations
46	+	-	11	0	2	9	1
47	+	+	13	1	0	12	8
48	+	+	7	0	1	6	0
49	+	+	-	-	-	0	0
50	+	+	-	-	-	0	0
51	+	+	-	-	-	0	0
52	+	+	9	0	0	9	0
53	+	+	-	-	-	0	0
54	+	+	-	-	-	0	0
55	+	+	11	0	0	11	0
56	+	+	8	1	0	7	0
57	+	+	12	0	0	12	0
58	+	+	7	2	0	5	0
59	+	+	10	0	0	10	0
60	+	+	6	0	0	6	0

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

APPENDIX D  
INDIVIDUAL MATERNAL AND FETAL PARAMETERS  
GROUP V  
DERMAL PYRAX WITH 10 PERCENT ABATE

Animal No.	Mated	Pregnant	Implantations	Resorptions Early	Total Late	No. of Fetuses	Dead	Alive Malformations
61	+	+	16	0	0	16	0	16 0
62	+	+	6	0	0	6	0	6 0
63	-	+	12	1	1	10	0	0 0
64	+	+	8	0	0	8	0	8 0
65	+	+	13	2	2	9	0	0 0
66	+	+	10	0	1	9	0	9 0
67	+	+	10	0	1	9	0	9 0
68	+	+	10	0	0	10	0	10 0
69	+	+	11	1	0	4	0	4 0
70	+	+	11	1	0	4	0	4 0
71	+	+	11	1	0	4	0	4 0
72	+	+	11	1	0	4	0	4 0
73	+	+	11	1	0	4	0	4 0
74	+	+	11	1	0	4	0	4 0
90	+	+	10	0	0	10	1	9 3

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

APPENDIX E

INDIVIDUAL MATERNAL AND FETAL PARAMETERS  
GROUP VI  
DERMAL TECHNICAL ABATE

Animal No.	Mated	Pregnant	Implantations	Resorptions	Total No. of Fetuses	Dead	Alive Malformations
75	+	8	0	0	8	0	8
76	-	-	-	-	-	-	-
77	+	8	4	0	4	0	4
78	Died before term	-	-	-	-	-	-
79	Died before term	-	-	-	-	-	-
80	Aborted	-	-	-	-	-	-
81	+	8	8	0	0	0	0
82	-	-	-	-	-	-	-
83	Died before term	-	-	-	-	-	-
84	+	8	0	0	8	1	8
85	Sacrificed before term (moribund)	-	-	-	-	-	-
86	+	6	2	0	4	0	4
87	Died before term	-	-	-	-	-	-
88	Died before term	-	-	-	-	-	-
89	+	9	0	0	9	0	9

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

APPENDIX 6  
INDIVIDUAL MATERNAL AND FETAL PARAMETERS  
GROUP VIII  
INTRAPERITONEAL 6-AN

Animal No.	Mated	Pregnant	Implantations	Resorptions	Total No. of Fetuses	Late Dead	Alive Malformations
			Died before term	Early			
106	+	+	10	5	0	5	0
107	+	+	11	11	0	0	5 17
108	+	+	-	-	-	0	0
109	+	+	-	-	-	0	0
110	+	+	-	23	0	0	0
111	+	+	-	12	0	0	0
112	+	+	-	-	-	0	0
113	+	+	-	6	3	3	9 8
114	+	+	-	5	0	0	0
115	+	+	-	5	0	0	0
116	+	+	-	4	0	0	0
117	+	+	-	-	-	0	0
118	+	+	-	7	4	3	6
119	+	+	-	7	0	0	0
120	+	+	-	9	6	3	3 13

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

APPENDIX F  
INDIVIDUAL MATERNAL AND FETAL PARAMETERS  
GROUP VII  
ORAL TECHNICAL ABATE

Animal No.	Mated	Pregnant	Implantations	Resorptions	Total No. of Fetuses	Dead	Alive Malformations
91	+	+	9	0	9	0	9 0
92	+	+	Died before term	10	0	10	0 0
93	+	+		11	3	0	8 0
94	+	+		11	3	0	8 0
95	+	+		10	3	0	8 0
96	+	+	Died before term		7	0	7 0
97	+	+	Died before term				
98	+	+	Died before term				
99	+	-		12	0	0	0 0
100	+	+	Died before term				
101	+	+	Died before term				
102	+	+	Died before term	9	3	6	6 -
103	+	+		8	0	8	1
104	+	+		9	0	9	0
105	+	+					

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

APPENDIX H

INDIVIDUAL MATERNAL AND FETAL PARAMETERS  
GROUP IX  
DERMAL PYRAZ WITH 2 PERCENT ABATE

Animal No.	Mated	Pregnant	Implantations	Early	Late	Resorptions	Total No. of Fetuses	Dead	Alive Malformations
121	+	+	10	1	0	9	0	9	
122	+	+	7	1	0	6	0	6	
123	+	+	9	2	0	7	0	7	
124	+	+	15	4	0	11	0	11	
125	+	-							
126	+	+	11	2	0	9	0	9	
127	+	+	10	2	0	8	0	8	
128	+	+	11	2	0	9	0	9	
129	+	Died before term	11	2	0	9	0	9	
130	+	+	11	1	0	10	0	10	
131	+	+	16	4	1	11	0	11	
132	+	+	13	1	0	12	0	12	
133	+	Died before term							
134	+	Died before term							
135	+	-							

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

APPENDIX I  
MEAN BODY WEIGHTS (kg) - Female Rabbits

Group Treatment	$\bar{x}$	SD	Day of Gestation				
			Day 4 Received	Day 6 Treatment Starts	Day 9	Day 18 Final Treatment	Day 30 Sacrifice
Dermal IV Pyrax Control	3.91	.38	3.98	.46	3.92	3.97	4.10
Dermal V Pyrax 10% ABATE	3.74	.38	3.68	.47	3.68	3.69	3.90
Dermal VI Tech ABATE	3.77	.31	3.71	.28	3.71	3.69	3.64
Oral VII ABATE	3.63	.24	3.56	.26	3.55	3.70	4.11
IP-6AN VIII Positive Control	3.53	.24	3.57	.27	3.63	3.47	3.76
Dermal IX Pyrax 2% ABATE	3.59	.26	3.57	.20	3.46	3.52	3.92

**APPENDIX J**  
**STATISTICAL ANALYSES OF BODY WEIGHT CHANGES**  
**(Percent body weight changes) - Analysis by Student "t"**

Group/Treatment	Day 30/Day 4				Day 18/Day 6				Days of Gestation				Day 6/Day 4				
	Complete Study Period	Treatment Period	Mean % Change ( $\pm$ SD)	DF	t	Day 30/Day 18 Post treatment Period	Mean % Change ( $\pm$ SD)	DF	t	Day 30/Day 18 Post treatment Period	Mean % Change ( $\pm$ SD)	DF	t	Day 6/Day 4 Preexposure Period	Mean % Change ( $\pm$ SD)	DF	t
IV Dermal Pyrax Control	105	-	-	7	-	100	-	-	-	102	-	-	-	102	-	-	-
V Dermal Pyrax 10% ABATE	104	26	0.19	8	-	99	27	0.07	6	106	26	1.25	5	98*	28	2.17	-
VI Dermal Technical ABATE	98	19	1.49	15	-	99	25	0.29	-	97	19	1.23	-	99	28	1.87	-
VII Oral ABATE	111*	21	2.20	6	-	103	24	0.99	-	112	21	1.66	-	98	27	2.01	-
VIII I.P. 6-AN (Positive Control)	108	25	0.92	9	-	98	26	1.07	-	106	21	2.49	-	101	28	0.30	-
IX Dermal Pyrax 2% ABATE	107	23	0.51	14	-	98	26	0.60	-	108	23	1.87	-	100	28	1.12	-

J-1

\* Significant differences ( $p < .05$ ) of body weight changes (%) comparing pyrax control with each of the various treatments.

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

APPENDIX K  
INDIVIDUAL MATERNAL BODY WEIGHTS(kg)  
GROUP IV  
DERMAL PYRAX CONTROL

Animal Number	DAY OF GESTATION												Final Treatment						
	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 23	Day 25	Day 30
46	4.3	4.45	4.37	4.40	4.26	4.36	4.34	4.40	4.42	4.44	4.49	4.56	4.52	4.43	4.43	4.41	4.63	4.71	4.63
47	3.9	3.94	3.94	3.98	3.83	3.75	3.65	3.55	3.50	DIED - 24 Mar	4.81	4.82	4.81	4.79	4.75	4.79	4.83	4.83	4.93
48	4.6	4.75	4.70	4.72	4.66	4.69	4.69	4.77	4.72	4.81	4.80	4.81	4.62	4.57	4.62	4.53	4.59	4.73	4.69
49	4.6	4.62	4.53	4.45	4.50	4.49	4.49	4.51	4.58	4.61	4.57	4.58	4.61	4.57	4.62	4.52	4.53	4.59	4.43
50	3.5	3.49	3.41	3.44	3.39	3.60	3.46	3.44	3.46	3.57	3.56	3.57	3.63	3.67	3.61	3.66	3.65	3.89	3.97
51	3.8	3.91	3.75	3.72	3.69	3.68	3.58	3.61	3.63	3.51	3.42	3.47	3.41	3.44	3.49	3.51	3.75	3.74	DIED
52	3.8	3.78	3.52	3.55	3.61	3.57	3.57	3.72	3.72	3.71	3.76	3.74	3.74	3.76	3.74	3.74	3.84	3.86	3.86
53	3.3	3.39	3.45	3.41	3.73	3.44	3.45	3.41	3.48	3.42	3.41	3.45	3.53	3.43	3.44	3.49	3.54	3.44	3.57
54	3.6	3.55	3.59	3.57	3.52	3.50	3.52	3.54	3.50	3.52	3.52	3.52	3.62	3.66	3.67	3.66	3.65	3.62	3.71
55	3.8	3.65	3.87	3.80	3.82	3.81	3.73	3.85	3.83	3.78	3.89	3.95	3.99	3.92	3.97	3.85	4.12	4.23	4.34
56	3.8	3.70	3.98	4.07	3.94	3.93	3.88	3.90	3.92	3.95	4.05	4.06	3.99	4.06	4.12	4.30	4.29	4.30	4.34
57	4.2	3.90	4.60	4.06	4.18	4.01	4.01	4.02	4.02	4.04	4.01	4.00	3.95	3.92	3.95	3.86	3.70	3.75	3.86
58	4.2	4.00	4.70	4.31	4.23	4.29	4.07	3.83	4.25	4.30	4.41	4.43	4.45	4.34	4.40	4.39	4.38	4.32	4.32
59	3.6	3.50	3.67	3.50	3.66	3.65	4.05	3.64	3.66	3.71	3.74	3.69	3.70	3.76	3.73	3.72	3.95	4.01	3.93
60	3.7	3.50	3.70	3.50	3.73	3.93	4.05	4.15	3.86	3.98	3.90	3.89	3.90	3.80	3.87	3.97	3.95	3.99	3.99
X	3.9	3.87	3.98	3.89	3.92	3.90	3.87	3.89	3.94	3.98	4.00	4.01	3.97	3.97	3.97	4.09	4.11	4.10	
+ SD	0.4	0.42	0.46	0.42	0.36	0.38	0.38	0.41	0.40	0.43	0.45	0.43	0.44	0.42	0.41	0.41	0.42	0.41	0.41

X-1

APPENDIX L  
INDIVIDUAL MATERNAL BODY WEIGHTS (kg)  
GROUP V  
DERMAL PYRAX WITH 10 PERCENT ABATE

Animal Number	DAY OF GESTATION												Day Final Treatment														
	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27			
61	3.5	3.45	3.3	3.42	3.45	3.48	3.52	3.51	3.43	3.48	3.51	3.47	3.44	3.44	3.42	3.58	3.64	3.64	3.64	3.64	3.64	3.64	3.64	3.64			
62	3.7	3.67	3.62	3.66	3.71	3.78	3.76	3.79	3.74	3.77	3.79	3.77	3.80	3.82	3.81	3.84	3.96	4.02	4.03	4.03	4.03	4.03	4.03	4.03	4.03		
63	3.3	3.14	3.07	3.05	2.97	2.67	2.72	2.69	2.63	2.70	2.65	2.86	2.96	2.84	3.08	3.06	3.36	3.44	3.50	3.50	3.50	3.50	3.50	3.50	3.50		
64	4.0	3.96	3.96	3.91	3.88	3.85	3.89	3.89	3.90	3.86	3.86	3.92	3.92	3.88	3.88	4.16	4.16	4.38	4.41	4.41	4.41	4.41	4.41	4.41	4.41		
65	3.8	3.84	3.83	3.80	3.70	3.75	3.78	3.86	3.93	3.83	3.87	3.92	3.93	3.83	3.90	3.94	4.10	4.12	4.17	4.17	4.17	4.17	4.17	4.17	4.17		
66	4.2	4.54	4.50	4.45	4.50	4.45	4.39	4.38	4.38	4.43	4.48	4.42	4.39	4.43	4.39	4.46	4.37	4.33	4.33	4.33	4.33	4.33	4.33	4.33	4.33		
67	4.4	4.50	4.40	4.47	4.26	4.39	4.38	4.38	4.38	4.35	4.28	4.18	4.13	4.08	4.14	4.13	4.11	4.29	4.45	4.45	4.45	4.45	4.45	4.45	4.45	4.45	
68	3.6	3.61	3.42	3.35	3.40	3.43	3.37	3.33	3.35	3.42	3.40	3.41	3.32	3.39	3.35	3.35	3.48	3.42	3.42	3.42	3.42	3.42	3.42	3.42	3.42		
69	3.7	3.50	3.67	3.67	3.71	3.69	3.66	3.68	3.68	3.73	3.75	3.81	3.77	3.70	3.76	3.76	3.85	3.93	3.93	3.93	3.93	3.93	3.93	3.93	3.93		
70	3.4	3.31	3.20	3.22	3.12	3.25	3.25	3.21	3.21	3.11	3.20	3.27	3.23	3.18	3.08	3.15	3.22	3.23	3.23	3.23	3.23	3.23	3.23	3.23	3.23		
71	3.6	3.40	3.30	3.31	3.37	3.42	3.42	3.61	3.49	3.48	3.48	3.55	3.51	3.46	3.56	3.57	3.59	3.72	3.72	3.72	3.72	3.72	3.72	3.72	3.72	3.72	
72	3.6	3.80	3.72	3.79	3.79	3.79	3.80	3.80	3.77	3.85	3.80	3.77	3.79	3.79	3.83	3.83	3.98	4.03	4.16	4.16	4.16	4.16	4.16	4.16	4.16	4.16	
73	3.6	3.70	3.60	3.67	3.63	3.66	3.57	3.64	3.64	3.59	3.61	3.59	3.60	3.53	3.51	3.53	3.57	3.72	3.76	3.76	3.76	3.76	3.76	3.76	3.76	3.76	
74	3.2	3.30	3.20	3.08	3.17	3.13	3.07	3.02	3.02	3.13	3.13	3.19	3.09	3.09	3.04	2.98	3.04	3.08	3.27	3.40	3.40	3.40	3.40	3.40	3.40	3.40	3.40
90	4.5	4.58	4.50	4.52	4.46	4.51	4.45	4.54	4.54	4.48	4.61	4.61	4.60	4.65	4.65	4.61	4.49	4.69	4.74	4.74	4.74	4.74	4.74	4.74	4.74	4.74	
$\bar{x}$	3.7	3.75	3.68	3.67	3.69	3.68	3.66	3.70	3.67	3.71	3.71	3.68	3.67	3.68	3.67	3.69	3.70	3.83	3.89	3.90	3.90	3.90	3.90	3.90	3.90	3.90	
$\pm SD$	0.4	0.45	0.47	0.48	0.46	0.45	0.46	0.50	0.48	0.51	0.51	0.51	0.47	0.48	0.50	0.47	0.45	0.42	0.44	0.53	0.44	0.42	0.44	0.42	0.44	0.44	

-1

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

APPENDIX M  
INDIVIDUAL MATERNAL BODY WEIGHTS (kg)  
GROUP VI  
DERMAL TECHNICAL ABATE

Animal Number	DAY OF GESTATION											Day 18 Final Treatment	Day 23	Day 25	Day 30	
	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14					
M-1	75	4.0	3.75	3.95	3.80	3.85	3.85	3.85	3.75	3.60	3.55	3.50	3.60	3.55	3.60	3.73
	76	4.4	4.10	4.30	4.30	4.35	4.30	4.30	4.50	4.60	4.65	4.70	4.70	4.65	4.70	4.05 DIED 8 Apr
	77	3.9	3.70	3.90	3.90	3.93	3.95	3.85	3.90	3.95	3.90	3.90	3.90	3.80	3.90	3.53
	78	3.4	3.10	3.30	3.15	3.20	3.30	3.30	3.35	3.35	3.35	3.30	3.05	2.90	2.85	3.58
	79	3.7	3.35	2.55	3.45	3.60	3.60	3.70	3.65	3.65	3.70	3.65	3.65	3.55	3.25	DIED 3 Apr
	80	4.1	3.75	4.00	4.05	4.10	4.10	4.10	4.20	4.10	4.15	4.15	4.15	4.05	4.00	3.65
	81	3.7	3.35	3.60	3.60	3.55	3.60	3.60	3.60	3.55	3.60	3.70	3.65	3.55	3.55	2.86
	82	3.5	3.25	3.65	3.60	3.70	3.75	3.75	3.80	3.85	3.90	3.80	3.85	3.70	3.80	3.51
	83	3.9	3.55	3.65	3.60	20 Mar	DIED	20	Mar							4.12
	84	3.7	3.40	3.65	3.70	3.70	3.80	3.90	3.85	3.90	3.95	3.95	3.85	3.80	3.99	3.90
	85	3.4	3.60	3.85	3.80	3.90	3.95	3.92	4.05	4.00	4.05	4.00	3.90	3.70	3.75	SACRIFICE D 4 Apr
	86	3.3	2.90	3.15	3.00	2.95	3.00	3.00	2.95	2.85	3.10	3.05	3.10	3.15	3.10	3.17
	87	4.1	3.75	3.80	3.75	3.75	3.65	3.50	3.45	3.45	3.35	3.25	3.20	DIED 28 Mar		
	88	3.6	3.30	3.55	3.55	3.60	3.55	3.50	3.55	3.55	3.45	3.55	3.60	3.55	3.35	
	89	3.8	3.40	3.70	3.70	3.60	3.60	3.80	3.80	3.85	3.90	3.95	3.95	3.90	4.00	4.10
$\bar{x}$	3.8	3.48	3.71	3.66	3.70	3.71	3.73	3.73	3.74	3.72	3.73	3.75	3.72	3.69	3.63	3.64
$\pm SD$	0.3	0.30	0.28	0.32	0.33	0.33	0.32	0.32	0.38	0.32	0.42	0.41	0.43	0.47	0.44	0.48
														0.36	0.30	0.47

M-1

APPENDIX N  
INDIVIDUAL MATERNAL BODY WEIGHTS (kg)  
GROUP VII  
ORAL TECHNICAL ABATE

Animal Number	DAY OF GESTATION												Day Final Treatment							
	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 23	Day 25	Day 30	
91	3.62	3.70	3.80	3.63	3.63	3.63	3.72	3.85	3.88	3.94	3.97	3.99	4.05	4.05	4.25	4.25	4.40			
92	3.37	3.40	3.46	3.38	3.38	3.38	DIED 2 May	3.74	3.78	3.80	3.84	3.87	3.87	3.90	3.92	3.94	3.94	3.95		
93	3.83	3.77	3.74	3.81	3.81	3.81	3.81	3.84	3.77	3.89	3.89	3.96	3.94	3.88	3.90	3.99	3.99	3.95		
94	3.87	3.90	3.93	3.75	3.75	3.75	3.80	3.84	3.77	3.89	3.89	3.96	3.94	3.88	3.88	3.88	3.88	3.90		
95	3.55	3.55	3.51	3.51	3.51	3.51	3.70	3.70	3.70	3.63	3.66	3.69	3.77	3.72	3.80	3.82	3.86	4.00	4.10	
96	3.92	3.83	3.87	3.90	3.90	3.90	3.99	3.99	3.99	3.94	3.94	3.95	3.92	3.96	4.01	4.01	4.05	4.11	4.10	
97	3.52	DEAD 28 Apr	3.25	3.13	2.97	2.97	2.97	2.80	2.80	2.70	2.77	2.76	2.60	2.50	2.32	2.20	2.12	DEAD		
98	3.28	3.47	3.45	3.47	3.47	3.47	3.47	3.47	3.47	3.47	3.47	3.47	3.47	3.47	3.47	3.47	3.47	3.47		
99	3.52	3.47	3.45	3.47	3.47	3.47	3.47	3.47	3.47	3.47	3.47	3.47	3.47	3.47	3.47	3.47	3.47	3.47		
100	3.60	3.60	3.64	3.62	3.62	3.62	3.62	3.62	3.62	3.65	3.65	3.68	3.71	3.72	3.72	3.76	3.76	3.76		
101	3.92	3.87	3.60	DEAD 30 Apr	3.26	3.26	3.26	3.26	3.31	3.29	3.31	3.33	3.30	3.38	3.34	3.36	3.38	3.38	3.62	
102	3.20	3.20	3.19	3.26	3.26	3.26	3.26	3.26	3.26	3.30	3.30	3.40	3.40	3.41	3.42	3.56	3.57	3.95	DEAD	
103	3.52	3.47	3.47	3.48	3.48	3.48	3.48	3.48	3.48	3.48	3.48	3.48	3.48	3.52	3.60	3.63	3.68	3.72	4.00	
104	3.77	3.63	3.24	3.30	3.30	3.30	3.30	3.30	3.30	3.30	3.43	3.43	3.43	3.43	3.48	3.63	3.68	3.80	4.10	
105	3.94	3.92	3.86	3.86	3.86	3.86	3.86	3.86	3.86	3.86	3.86	3.86	3.86	3.86	3.86	3.90	4.02	4.04	4.16	
$\bar{x}$	3.63	3.62	3.56	3.55	3.56	3.55	3.55	3.55	3.58	3.59	3.63	3.64	3.69	3.70	3.69	3.70	3.71	3.99	4.02	4.11
$\pm SD$	0.24	0.23	0.26	0.27	0.28	0.27	0.27	0.27	0.32	0.31	0.35	0.33	0.34	0.40	0.43	0.48	0.51	0.54	0.17	0.18
																			0.16	

-1

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

APPENDIX 0  
INDIVIDUAL MATERNAL BODY WEIGHTS (kg)  
GROUP VIII  
INTRAPERITONEAL 6-AN

Animal Number	DAY OF GESTATION																	
	Day 4	Day 5	Day 6	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 23	Day 25	Day 30
106	3.80	3.94	3.99	3.70	3.66	3.65	3.66	3.98	3.96	3.96	3.60	3.63	3.99	DEAD	10 May			
107	3.46	3.91	3.99	3.98	3.96	3.96	3.98	3.18	3.09	3.03	4.02	3.99	4.10	4.15	4.25	4.31	4.45	
108	3.64	3.47	3.37	3.25	3.18	3.18	3.18	2.92	2.92	3.03	3.27	3.27	3.27	3.25	3.32	3.38	3.50	
109	3.59	3.42	3.42	3.54	3.35	3.36	3.35	3.35	3.35	3.30	3.17	3.92	3.32	3.37	3.74	3.79	3.90	
110	3.90	3.83	3.83	3.75	3.58	3.53	3.48	3.53	3.53	3.33	3.43	3.75	3.65	3.65	3.55	3.67	3.67	3.80
111	3.75	3.91	3.91	3.88	3.64	3.73	3.82	3.73	3.88	3.87	3.88	3.92	3.94	3.80	3.87	3.98	4.15	
112	3.20	3.08	3.08	2.97	2.81	2.85	2.71	2.85	2.85	2.64	2.68	2.97	2.71	2.80	2.80	2.96	2.97	3.15
113	3.30	3.41	3.41	3.34	3.14	2.92	2.92	2.92	2.92	2.92	3.10	3.34	3.45	3.45	3.64	3.45	3.50	3.55
114	3.79	3.35	3.35	3.70	3.55	3.48	3.34	3.48	3.48	3.48	3.51	3.70	3.62	3.64	3.82	3.74	3.79	3.90
115	3.14	3.45	3.45	3.64	3.48	3.35	3.31	3.35	3.35	3.13	3.12	3.64	3.28	3.29	3.12	3.43	3.48	3.60
116	3.32	3.39	3.39	3.18	3.09	3.15	3.05	3.15	3.15	3.04	3.13	3.18	2.96	2.88	2.86	3.15	3.20	3.35
117	3.72	3.91	3.91	3.95	3.69	3.75	3.81	3.75	3.75	3.69	3.59	3.95	3.59	3.59	3.70	3.71	3.80	4.00
118	3.48	3.58	3.58	3.48	3.48	3.39	3.45	3.39	3.39	3.53	3.54	3.78	3.63	3.66	3.80	3.75	3.79	3.85
119	3.25	3.31	3.31	3.46	3.20	3.11	3.08	3.11	3.11	3.44	3.15	3.45	3.24	3.29	3.35	3.45	3.47	3.60
120	3.61	3.66	3.66	3.61	3.55	3.34	3.29	3.34	3.34	3.02	3.42	3.61	3.65	3.48	3.82	3.80	3.84	3.90
$\bar{x}$	3.53	3.57	3.57	3.63	3.45	3.38	3.36	3.38	3.38	3.33	3.36	3.63	3.46	3.47	3.50	3.60	3.64	3.76
$\pm SD$	0.24	0.27	0.27	0.31	0.30	0.35	0.31	0.38	0.35	0.31	0.36	0.37	0.39	0.33	0.34	0.33	0.34	0.33

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

APPENDIX P  
INDIVIDUAL MATERNAL BODY WEIGHTS (kg)  
GROUP IX  
DERMAL PYRAX WITH 2 PERCENT ABATE

Animal Number	DAY OF GESTATION													Day 30 Final Treatment				
	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 23	Day 25
121	3.74	3.63	3.75	3.58	3.39	3.30	3.42	3.39	3.22	3.28	3.34	3.35	3.35	3.34	3.38	3.53	3.53	3.68
122	3.43	3.16	3.37	3.37	3.30	3.43	3.49	3.45	3.48	3.51	3.56	3.52	3.60	3.58	3.61	3.79	3.75	
123	3.96	3.87	3.83	3.80	3.85	3.84	3.88	3.84	3.87	3.86	3.84	3.97	4.06	4.00	4.04	4.41	4.52	
124	3.44	3.39	3.46	3.43	3.42	3.35	3.40	3.47	3.54	3.52	3.59	3.57	3.60	3.63	3.63	3.63	4.03	
125	3.69	3.65	3.57	3.56	3.42	3.37	3.34	3.35	3.28	3.30	3.22	3.08	3.02	3.04	3.02	2.96	2.71	2.58
126	3.89	3.68	3.72	3.74	3.66	3.65	3.62	3.55	3.60	3.56	3.54	3.52	3.50	3.47	3.53	3.64	3.88	4.00
127	3.33	3.20	3.22	3.18	3.29	3.28	3.34	3.36	3.30	3.31	3.38	3.38	3.39	3.46	3.45	3.46	3.57	3.80
128	3.94	3.74	3.85	3.82	3.78	3.70	3.73	3.63	3.67	3.59	3.61	3.49	3.47	3.55	3.57	3.51	3.53	3.88
129	3.06	3.56	3.64	3.49	3.52	3.46	3.53	3.55	3.59	3.44	3.40	3.23	3.11	2.89	2.84	DIED 11 May	3.70	
130	3.49	3.37	3.48	3.46	3.49	3.39	3.53	3.57	3.63	3.62	3.65	3.50	3.68	3.76	3.79	3.82	3.77	3.97
131	3.76	3.48	3.61	3.37	3.29	3.42	3.62	3.59	3.66	3.64	3.71	3.84	3.85	3.85	3.92	3.96	4.01	4.29
132	3.69	3.64	3.64	3.61	3.57	3.58	3.73	3.74	3.72	3.87	3.70	3.74	3.82	3.83	3.70	3.86	4.08	4.31
133	3.42	3.36	3.33	3.33	3.35	3.28	3.11	3.19	2.90	2.87	2.77	2.59	2.40	2.32	DIED 10 May			
134	3.36	3.41	3.41	3.30	3.38	3.29	3.28	3.31	3.36	3.40	3.45	3.39	3.30	3.29	3.21	2.88	DIED 12 May	
135	3.67	3.58	3.71	3.79	3.75	3.65	3.68	3.67	3.70	3.68	3.76	3.65	3.68	3.82	3.73	3.64	3.60	3.69
$\bar{x}$	3.59	3.51	3.57	3.53	3.51	3.46	3.51	3.52	3.52	3.49	3.45	3.45	3.45	3.45	3.45	3.52	3.54	3.62
$\pm SD$	0.26	0.20	0.20	0.19	0.19	0.18	0.21	0.17	0.23	0.24	0.27	0.31	0.39	0.45	0.36	0.32	0.29	0.43
																3.79	3.92	0.53

APPENDIX Q

RBC CHOLINESTERASE ACTIVITY  
COMPARISON WITH TIME OF VARIOUS TREATMENTS WITH PYRAX CONTROL

Group Treatment	Mean +SD RBC Cholinesterase Activity Values			
	Comparison with Pyrax Control			
	Day of Gestation			
	Day 6 Pretest	Day 10 Test Day 4	Day 19 Test Day 13	Day 30 Sacrifice Day
IV Pyrax Control	7.52 2.60	8.40 2.87	8.12 2.64	8.69 2.15
V Dermal Pyrax 10% ABATE	7.57 2.15 <i>n</i> = 28 <i>t</i> = 0.05	8.35 2.24 <i>n</i> = 28 <i>t</i> = 0.06	4.68* 1.89 <i>n</i> = 26 <i>t</i> = 4.01	5.79* 1.44 <i>n</i> = 27 <i>t</i> = 4.30
VI Dermal Technical ABATE	7.74 1.87 <i>n</i> = 28 <i>t</i> = 0.27	7.43 2.52 <i>n</i> = 27 <i>t</i> = 0.97	2.77* 2.63 <i>n</i> = 24 <i>t</i> = 5.18	2.40* 0.34 <i>n</i> = 20 <i>t</i> = 8.14
VII Oral Technical ABATE	8.06 2.31 <i>n</i> = 27 <i>t</i> = 0.59	7.18 2.37 <i>n</i> = 25 <i>t</i> = 1.18	4.78* 1.30 <i>n</i> = 23 <i>t</i> = 3.97	5.66* 1.99 <i>n</i> = .22 <i>t</i> = 3.51
VIII I.P. 6-AN	9.35 2.38 <i>n</i> = 28 <i>t</i> = 2.01	10.09 2.43 <i>n</i> = 28 <i>t</i> = 1.74	10.24*† 2.33 <i>n</i> = 25 <i>t</i> = 2.21	9.90 2.31 <i>n</i> = 26 <i>t</i> = 1.44
IX Dermal Pyrax 2% ABATE	8.88 2.02 <i>n</i> = 28 <i>t</i> = 1.60	9.03 2.16 <i>n</i> = 28 <i>t</i> = 0.68	9.95 2.25 <i>n</i> = 23 <i>t</i> = 1.85	9.47 2.11 <i>n</i> = 24 <i>t</i> = 0.93

\* Significantly different from Pyrax control value significantly at p<.05,  
as determined by student's "t" test.

† Cholinesterase activity value significantly higher than control.

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

INDIVIDUAL MATERNAL

APPENDIX R

RBC CHOLINESTERASE ACTIVITY (GARRY AND ROUTH UNITS)

GROUP IV  
DERMAL PYRAX CONTROL

Animal Number	Pretest	Day of Gestation			Sacrificed
		Day 6	Day 10	Day 19	
46	8.4	11.7	8.5	7.8	
47	3.4	3.8	Dead	-	
48	9.0	9.5	10.3	9.6	
49	7.2	8.1	Missed	8.2	
50	7.4	8.7	8.4	11.0	
51	7.4	7.7	8.3	8.4	
52	6.9	8.8	7.7	9.2	
53	10.7	12.1	11.7	9.9	
54	8.9	9.8	9.5	10.2	
55	3.9	4.0	3.1	4.5	
56	12.7	12.9	11.8	12.8	
57	3.8	3.8	3.6	5.0	
58	6.4	7.3	6.9	7.5	
59	10.0	10.2	9.1	9.1	
60	6.7	7.6	6.7	7.3	
$\bar{x}$		7.52	8.40	8.12	8.69
$\pm SD$		2.60	2.87	2.64	2.15

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

INDIVIDUAL MATERNAL

APPENDIX S

RBC CHOLINESTERASE ACTIVITY (GARRY AND ROUTH UNITS)  
GROUP V  
DERMAL PYRAX WITH 10 PERCENT ABATE

Animal Number	Pretest	Day of Gestation		
		Day 6	Day 10	Day 19
61	8.3	8.8	3.2	3.9
62	7.2	8.0	7.3	8.2
63	9.3	10.4	4.8	7.2
64	6.7	7.7	3.8	5.8
65	9.6	10.2	4.0	5.3
66	5.8	7.7	7.6	7.7
67	3.1	3.9	3.0	4.4
68	10.8	11.5	6.7	6.9
69	9.7	10.5	5.0	5.5
70	4.7	5.4	2.0	3.7
71	9.0	9.4	7.5	7.6
72	7.0	7.1	4.1	6.0
73	5.9	6.4	4.8	5.0
74	9.6	11.4	4.7	5.2
90	6.8	6.8	1.7	4.4
$\bar{x}$		7.57	8.35	4.68
$\pm SD$		2.84	2.24	1.89
				5.79
				1.44

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

INDIVIDUAL MATERNAL

APPENDIX T

RBC CHOLINESTERASE ACTIVITY (GARRY AND ROUTH UNITS)

GROUP VI  
DERMAL TECHNICAL ABATE

Animal Number	Pretest	Day of Gestation			Sacrificed
		Day 6	Day 10	Day 19	
75	5.4	3.4		1.1	2.5
76	8.8	10.5		1.8	Dead
77	7.4	8.0		1.1	2.8
78	9.7	9.0		1.5	Dead
79	7.3	9.8		3.4	Dead
80	9.3	4.3		0.71	2.1
81	6.4	7.5		4.1	2.3
82	6.4	6.1		2.9	3.0
83	6.2	Dead			
84	9.7	10.1		10.1	2.2
85	9.6	8.5		1.5	2.2
86	6.3	3.9		0.82	Dead
87	4.3	4.4		Dead	
88	10.5	9.5		1.5	Dead
89	8.8	9.0		5.5	2.1
$\bar{x}$	7.74	7.43		2.77	2.40
$\pm$	2.23	2.52		2.63	0.34

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

INDIVIDUAL MATERNAL

APPENDIX U

RBC CHOLINESTERASE ACTIVITY (GARRY AND ROUTH UNITS)  
GROUP VII  
ORAL TECHNICAL ABATE

Animal Number	Pretest	Day of Gestation			Sacrificed
		Day 6	Day 10	Day 19	
91	7.7	7.9	5.6	5.8	
92	9.1	DEAD	-	-	
93	4.4	4.1	3.7	3.4	
94	6.7	6.4	4.0	3.3	
95	9.4	8.1	5.7	5.5	
96	7.6	6.6	3.8	4.4	
97	Dead	-	-	-	
98	4.7	2.7	4.8	-	
99	5.0	5.9	4.2	3.7	
100	10.9	9.4	5.6	8.7	
101	10.0	DEAD	-	-	
102	7.1	5.8	4.0	-	
103	9.0	9.7	3.8	6.1	
104	11.9	9.0	4.0	7.4	
105	9.4	10.6	8.1	8.3	
<u><math>\bar{x}</math></u>		8.06	7.18	4.78	5.66
<u><math>\pm SD</math></u>		2.31	2.37	1.30	1.99

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

INDIVIDUAL MATERNAL

APPENDIX V

RBC CHOLINESTERASE ACTIVITY (GARRY AND ROUTH UNITS)  
GROUP VIII  
INTRAPERITONEAL 6-AN

Animal Number	Pretest	Day of Gestation			Sacrificed
		Day 6	Day 10	Day 19	
		Test Day 4	Test Day 13		
106	13.3	12.2	DEAD	-	
107	10.2	10.7	10.4	10.3	
108	10.6	11.8	11.7	10.7	
109	7.4	8.6	9.1	8.4	
110	7.4	8.5	7.9	8.0	
111	12.4	15.4	14.6	14.9	
112	9.7	10.8	12.0	10.2	
113	7.8	8.3	9.1	9.7	
114	7.6	8.6	9.6	9.7	
115	10.1	9.9	10.7	9.8	
116	13.4	13.9	14.5	14.7	
117	9.7	10.0	10.0	8.7	
118	6.4	7.2	7.1	7.8	
119	8.3	8.8	9.5	8.2	
120	5.9	6.7	7.2	7.5	
$\bar{x}$	9.35	10.09	10.24	9.90	
$\pm SD$	2.38	2.43	2.33	2.31	

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

INDIVIDUAL MATERNAL

APPENDIX W

RBC CHOLINESTERASE ACTIVITY (GARRY AND ROUTH UNITS)  
GROUP IX  
DERMAL PYRAX WITH 2 PERCENT ABATE

Animal Number	Pretest	Day of Gestation			Sacrificed
		Day 6	Day 10	Day 19	
121	9.7	10.2		12.2	10.2
122	10.5	9.6		11.7	10.0
123	5.8	5.1		7.1	6.9
124	5.7	6.0		7.4	8.0
125	8.0	8.0		8.4	7.1
126	6.8	7.1		7.5	7.7
127	10.1	9.7		10.9	11.9
128	6.8	6.9		7.4	7.9
129	9.8	9.6		DEAD	-
130	11.0	12.6		12.8	14.0
131	10.2	8.9		10.4	9.6
132	10.6	11.1		10.8	9.5
133	8.1	12.0		DEAD	-
134	7.8	8.1		DEAD	-
135	12.3	10.5		12.8	10.8
$\bar{x}$	8.88	9.03		9.95	9.47
$\pm SD$	2.02	2.16		2.25	2.11

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

APPENDIX X

PLASMA CHOLINESTERASE ACTIVITY  
COMPARISON WITH TIME OF VARIOUS TREATMENT WITH PYRAX CONTROL

Group	Treatment	Mean ( $\pm$ SD) Plasma Cholinesterase Activity Values			
		Comparison With Pyrax Control			
		Day of Gestation			
		Day 6	Day 10	Day 19	Day 30 Sacrifice Day
		Pretest	Test Day 4	Test Day 13	
IV	Pyrax Control	4.97 1.18	3.34 0.81	3.75 1.01	2.71 1.08
V	Dermal Pyrax 10% ABATE	5.01 1.01 <i>n</i> = 28 <i>t</i> = 0.08	3.07 1.06 <i>n</i> = 28 <i>t</i> = 0.77	2.52* 1.01 <i>n</i> = 26 <i>t</i> = 3.24	2.97 0.99 <i>n</i> = 27 <i>t</i> = 0.67
VI	Dermal Technical ABATE	5.56 0.90 <i>n</i> = 28 <i>t</i> = 1.53	2.97 1.14 <i>n</i> = 27 <i>t</i> = 1.01	1.34* 0.90 <i>n</i> = 24 <i>t</i> = 6.45	1.54* 0.63 <i>n</i> = 20 <i>t</i> = 2.80
VII	Oral Technical ABATE	5.59 0.91 <i>n</i> = 27 <i>t</i> = 1.56	4.27*† 0.99 <i>n</i> = 25 <i>t</i> = 2.68	3.53 0.90 <i>n</i> = 23 <i>t</i> = 0.58	2.97 1.08 <i>n</i> = .22 <i>t</i> = 0.57
VIII	IP 6-AN	5.75 1.31 <i>n</i> = 28 <i>t</i> = 1.70	5.11*† 1.35 <i>n</i> = 28 <i>t</i> = 4.36	5.38*† 1.34 <i>n</i> = 25 <i>t</i> = 3.54	4.57*† 1.19 <i>n</i> = 26 <i>t</i> = 4.32
IX	Dermal Pyrax 2% ABATE	5.56 1.15 <i>n</i> = 28 <i>t</i> = 1.38	4.56*† 1.13 <i>n</i> = 28 <i>t</i> = 3.41	4.88*† 0.74 <i>n</i> = 23 <i>t</i> = 3.16	2.75 0.84 <i>n</i> = 24 <i>t</i> = 0.09

\* Significantly different from Pyrax control values at  $p < .05$  as determined by student's "t" test.

† Cholinesterase activity significantly higher than control.

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

INDIVIDUAL MATERNAL

APPENDIX Y

PLASMA CHOLINESTERASE ACTIVITY (GARRY AND ROUTH UNITS)  
GROUP IV  
DERMAL PYRAX CONTROL

Animal	Pretest	Day of Gestation			Sacrificed
		Day 6	Day 10	Day 19	
46	4.9	3.3	4.4	3.7	
47	5.6	4.6	Dead	Dead	
48	3.9	2.6	2.6	2.0	
49	4.0	2.7	Missed	1.7	
50	4.0	2.2	3.0	2.0	...
51	5.8	3.9	5.3	4.0	
52	5.1	4.3	4.1	2.7	
53	6.0	4.1	4.1	4.1	
54	3.6	2.2	2.9	2.1	
55	4.7	3.3	2.8	1.9	
56	4.0	2.3	2.3	1.8	
57	5.8	3.4	4.1	2.4	
58	5.8	3.9	4.2	2.4	
59	3.6	3.1	3.5	1.9	
60	7.8	4.2	5.5	4.7	
$\bar{x}$	4.97	3.34	3.75	2.71	
$\pm SD$	1.18	0.81	1.01	1.08	

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

APPENDIX Z

INDIVIDUAL MATERNAL

PLASMA CHOLINESTERASE ACTIVITY (GARRY AND ROUTH UNITS)

GROUP V

DERMAL PYRAX WITH 10 PERCENT ABATE

Animal	Pretest	Day of Gestation			Sacrificed
		Day 6	Day 10	Day 19	
			Test Day 4	Test Day 13	
61	6.2		3.4	2.0	1.7
62	5.0		2.4	2.9	2.2
63	5.8		1.5	3.2	3.8
64	4.0		2.5	1.5	2.5
65	4.8		3.8	2.6	3.0
66	3.9		2.8	2.8	2.2
67	7.3		5.7	2.8	3.9
68	4.8		3.5	2.9	2.5
69	4.4		3.3	1.6	2.0
70	4.8		3.3	1.8	3.4
71	4.0		2.9	2.1	3.5
72	6.3		3.4	3.5	4.3
73	5.4		3.9	5.0	4.7
74	4.1		2.5	2.3	3.5
90	4.3		1.2	0.7	1.4
$\bar{x}$	5.01		3.07	2.52	2.97
$\pm SD$	1.01		1.06	1.01	0.99

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

INDIVIDUAL MATERNAL

APPENDIX AA

PLASMA CHOLINESTERASE ACTIVITY (GARRY AND ROUTH UNITS)  
GROUP VI  
DERMAL TECHNICAL ABATE

Animal	Pretest	Day of Gestation			Sacrificed
		Day 6	Day 10	Day 19	
			Test Day 4	Test Day 13	
75	5.2		1.2	1.0	1.4
76	5.1		2.6	0.5	DEAD
77	5.9		3.5	0.6	1.4
78	5.6		2.1	0.7	DEAD
79	5.7		3.1	2.5	DEAD
80	5.0		1.2	0.5	1.3
81	4.6		2.6	1.5	1.8
82	6.3		3.1	1.3	3.0
83	6.6	DEAD			
84	4.3		3.4	3.1	1.1
85	7.0		3.9	1.1	DEAD
86	6.6		2.5	1.7	1.2
87	5.7		5.7	DEAD	
88	3.8		2.9	0.4	DEAD
89	6.0		3.8	2.6	1.1
$\bar{x}$	5.56		2.97	1.34	1.54
$\pm SD$	0.90		1.14	0.90	0.63

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

INDIVIDUAL MATERNAL

APPENDIX BB

PLASMA CHOLINESTERASE ACTIVITY (GARRY AND ROUTH UNITS)  
GROUP VII  
ORAL ABATE

Animal	Pretest	Day of Gestation			
		Day 6	Day 10	Day 19	Day 30
		Test Day 4	Test Day 13	Sacrificed	
91	3.9	3.6	3.6	1.3	
92	5.6	DEAD	-	-	
93	6.0	5.3	3.5	3.3	
94	5.7	5.2	4.0	2.0	
95	4.7	3.3	2.8	2.5	
96	6.6	4.7	3.0	3.4	
97	Dead	-	-	-	
98	5.5	2.4	1.9	Dead	
99	6.3	4.6	5.3	5.3	
100	4.6	3.5	3.4	3.5	
101	4.5	DEAD	-	-	
102	6.4	4.6	3.9	-	
103	5.1	4.4	2.6	3.3	
104	6.6	3.7	3.9	2.6	
105	6.7	5.9	4.5	2.5	
$\bar{x}$	5.59	4.27	3.53	2.97	
$\pm SD$	0.91	0.99	0.90	1.08	

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

APPENDIX CC  
INDIVIDUAL MATERNAL  
PLASMA CHOLINESTERASE ACTIVITY (GARRY AND ROUTH UNITS)  
GROUP VII  
INTRAPERITONEAL 6-AN

Animal	Pretest	Day of Gestation			Sacrificed
		Day 6	Day 10	Day 19	
		Test Day 4	Test Day 13		
106	4.7	4.6		Dead	
107	4.9	3.9	3.9		3.0
108	9.7	9.6	9.1		7.6
109	6.7	5.5	5.5		5.5
110	5.0	4.1	4.3		3.8
111	6.5	4.8	7.3		4.5
112	5.3	4.2	5.2		5.5
113	5.2	4.7	5.1		3.9
114	6.1	4.8	4.9		3.7
115	5.0	4.6	5.3		5.3
116	5.3	5.7	5.5		4.7
117	4.4	4.9	4.7		4.7
118	5.8	4.8	4.6		3.9
119	6.6	5.8	5.5		4.8
120	5.0	4.7	4.4		3.1
$\bar{x}$	5.75	5.11	5.38		4.57
$\pm SD$	1.31	1.35	1.34		1.19

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

INDIVIDUAL MATERNAL

APPENDIX DD

PLASMA CHOLINESTERASE ACTIVITY (GARRY AND ROUTH UNITS)  
GROUP IX  
DERMAL PYRAX WITH 2 PERCENT ABATE

Animal	Pretest	Day of Gestation			Sacrificed
		Day 6	Day 10	Day 19	
			Test Day 4	Test Day 13	
121	4.5		3.6	4.0	1.4
122	5.7		4.5	5.0	2.7
123	6.4		5.5	5.0	2.4
124	6.5		4.5	4.9	2.5
125	4.8		3.4	5.8	4.5
126	5.8		5.5	6.0	2.8
127	6.9		4.9	4.8	3.1
128	5.2		4.8	3.8	3.5
129	5.6		4.3	DEAD	-
130	7.0		5.4	5.3	2.4
131	6.9		5.7	5.6	2.3
132	5.2		4.6	4.4	1.8
133	2.9		1.6	DEAD	-
134	5.9		6.1	DEAD	-
135	4.1		4.0	3.9	3.6
$\bar{x}$	5.56		4.56	4.88	2.75
+ SD	1.15		1.13	0.74	0.84

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

APPENDIX EE  
MATERNAL BRAIN CHOLINESTERASE ACTIVITY (GARRY AND ROUTH UNITS)  
AT TERMINATION OF PREGNANCY (Day 30 of Gestation)

Animal Number	Activity	Animal Number	Group IV			Group V			Group VI			Group VII			Group VIII			Group IX			
			Dermal Pyrax Control	(1.81 gm/kg/day)	10% ABATE	(1.81 gm/kg/day)	Dermal Pyrax ABATE	(0.14 ml/kg/day)	Technical ABATE	(0.14 ml/kg/day)	Oral ABATE	(32 mg/kg/day)	Positive Control	IP 6-AN	Activity	Animal Number	Activity	Animal Number	Activity	Animal Number	Activity
46	46.3	61	58.3	75	39.3	91	47.6	107	53.0	121	49.2										
48	46.5	62	53.1	77	40.6	93	49.0	108	52.9	122	48.7										
49	49.0	63	57.9*	80	40.6	94	48.3	109	47.0	123	51.7										
50	47.3	64	45.9	81	42.0	95	52.6	110	55.2	124	57.3										
52	49.5	65	44.8	82	38.7	96	53.6	111	48.7	125	54.3										
53	48.1	66	46.5	84	37.6	99	47.4	112	47.5	126	53.4										
54	45.2	67	50.5	86	30.9	100	45.3	113	51.1	127	53.6										
55	47.8	68	52.8	89	41.3	103	48.6	114	50.7	128	49.1										
56	48.9	69	51.1				104	45.4	115	55.3	130	51.8									
57	50.6	70	50.6				105	52.0	116	54.6	131	47.4									
58	55.7	71	52.0						117	55.5	132	48.1									
59	52.7	72	55.0						118	59.8	135	52.9									
60	45.7	73	55.5						119	53.7											
		74	45.5						120	51.3											
			90																		

EE-1

APPENDIX FF

MATERNAL BRAIN CHOLINESTERASE ACTIVITY (GARRY AND ROUTH UNITS)  
COMPARISON WITH TIME OF VARIOUS TREATMENTS WITH  
PYRAX CONTROL

Group	Treatment	Mean (SD)	Brain Cholinesterase Activity Values at End of Study (Day 30 of Pregnancy)	DF	t
Group IV	Dermal Pyrax Control	48.7 2.9		-	-
Group V	Dermal Pyrax 10% ABATE	51.2 4.4		26	1.75
Group VI	Dermal Technical ABATE	38.9 3.5		19	6.89*
Group VII	Oral ABATE	49.0 2.9		21	0.24
Group VIII	IP 6-AN	51.3 3.5		25	3.09*†
Group IX	Dermal Pyrax 2% ABATE	51.5 3.0		23	2.31*†

\* Significantly different from Pyrax control values at p<.05 as determined by students "t" test.

† Cholinesterase activity values higher than control.

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

APPENDIX GG

MEAN FETAL BODY WEIGHT AND LENGTH PER DOE

Group	Animal Number	Weight (gm)		Length (cm)	
		$\bar{X}$	$\pm SD$	$\bar{X}$	$\pm SD$
IV	46	-	-	-	-
Dermal	48	44.4	6.6	8.5	0.5
(Control Pyrax)	49	42.2	4.5	8.5	0.3
	50	55.4	3.8	8.2	0.1
	51	-	-	-	-
	52	40.4	3.6	8.7	0.5
	53	-	-	-	-
	54	46.3	12.9	8.5	0.5
	55	63.1	3.1	9.1	0.6
	56	44.9	8.9	8.9	0.5
	57	57.0	3.9	9.3	0.6
	58	50.9	5.7	9.4	0.8
	59	51.9	8.2	8.8	0.4
	60	-	-	-	-
V	61	37.8	6.5	8.1	0.7
Dermal Pyrax	62	58.0	4.6	8.9	0.2
10% ABATE	63	-	-	-	-
	64	45.4	8.3	8.4	0.7
	65	53.8	10.4	9.0	0.8
	66	53.9	5.1	8.8	0.7
	67	49.2	10.5	8.9	0.7
	70	-	-	-	-
	71	-	-	-	-
	72	54.8	5.6	9.6	0.5
	73	-	-	-	-
	74	-	-	-	-
	90	48.9	12.0	8.5	0.7
VI	75	33.2	6.4	8.7	0.8
Dermal Technical	76	-	-	-	-
ABATE	77	46.1	15.2	9.9	1.6
	81	-	-	-	-
	82	-	-	-	-
	84	41.6	4.5	8.4	0.4
	86	36.8	3.5	8.2	0.3
	89	46.1	7.2	8.4	0.4

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84,  
Apr 83

Group	Animal Number	Weight (gm)		Length (cm)	
		$\bar{x}$	$\pm SD$	$\bar{x}$	$\pm SD$
VII Oral ABATE (32 mg/kg/day)	91	53.6	3.5	9.1	0.5
	93	40.4	6.6	8.7	0.7
	94	54.3	4.7	9.3	0.4
	95	49.5	8.8	9.4	0.6
	96	47.4	5.1	9.1	0.4
	99	-	-	-	-
	100	-	-	-	-
	103	46.2	4.6	9.1	0.7
	104	46.4	4.9	9.1	0.3
	105	59.8	9.1	9.7	0.5
VIII IP 6-AN	107	44.1	3.7	8.2	0.8
	108	-	-	-	-
	109	-	-	-	-
	110	-	-	-	-
	111	-	-	-	-
	112	-	-	-	-
	113	36.1	3.3	7.5	0.3
	114	21.6	5.2	6.6	0.6
	115	-	-	-	-
	116	-	-	-	-
	117	-	-	-	-
	118	35.1	14.3	6.9	1.3
	119	-	-	-	-
IX Dermal Pyrax 2% ABATE	120	41.5	5.3	7.1	1.5
	121	51.0	6.2	9.2	0.8
	122	61.8	3.9	9.6	0.6
	123	61.7	4.3	9.4	0.6
	124	49.9	4.3	9.8	0.6
	125	-	-	-	-
	126	49.0	5.2	8.9	0.7
	127	53.5	5.8	9.4	0.9
	128	44.9	4.9	8.6	0.8
	130	54.0	3.4	9.6	0.5
	131	55.5	5.9	9.6	0.6
	132	48.6	9.8	9.0	0.7
	135	-	-	-	-

Phase 4, Toxicological Assessment of ABATE, Study No. 75-51-1302-84, Apr 83

APPENDIX HH

BIBLIOGRAPHY

1. Shardein, J. L., E. T. Woosley, M. A. Peltzer and D. H. Kaump, "Congenital malformations induced by 6-aminonicotinamide in rabbit kits", Experimental and Molecular Pathology, 6, pp 335-346 (1967).
2. Garry, P. H. and J. I. Routh, "A micro method for serum cholinesterase", Clin Chem II, p 91 (1965).
3. Wilson, J. G. and J. Warkany, Teratology, Principles and Techniques, pp 262-277 (1967). The University of Chicago Press, Chicago, Illinois.
4. Thompson, S. W., Selected Histochemical and Histopathological Methods, pp 12-13 (1966), Charles C. Thomas, Publisher, Springfield, Illinois.
5. Dawson, A. B., "A note on the staining of the skeleton of cleared specimens with alizerin red S", Stain Tech 1, pp 123-124 (1926).

